UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/635,108	08/05/2003	Stephen Scaringe	13561	6956

23719 7590 01/27/2005

KALOW & SPRINGUT LLP
488 MADISON AVENUE
19TH FLOOR
NEW YORK, NY 10022

EXAMINER	
SISSON, BRADLEY L	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 01/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/635,108	SCARINGE, STEPHEN	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-23* is/are rejected.

7)☒ Claim(s) *11-22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/3, 7/2, 9/27/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Specification

1. The amendment filed 27 September 2004 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material, which is not supported by the original disclosure, is as follows: The amendments to Paragraph 0056.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Objections

2. A series of singular dependent claims is permissible in which a dependent claim refers to a preceding claim which, in turn, refers to another preceding claim.

3. A claim that depends from a dependent claim should not be separated by any claim, which does not also depend from said dependent claim. In the instant case, claims 11-22 are separated from claim 9 by independent claim 10. It should be kept in mind that a dependent claim may refer to any preceding independent claim. In general, applicant's sequence will not be changed. See MPEP § 608.01(n).

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 9-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Attention is directed to the decision in *University of Rochester v. G.D. Searle & Co.* 68 USPQ2D 1424 (Fed. Cir. 2004) at 1428:

> To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. Vas-Cath, 935 F.3d at 1563; see also Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572 [41 USPQ2d 1961] (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention"); In re Gosteli, 872 F.2d 1008, 1012 [10 USPQ2d 1614] (Fed. Cir. 1989) ("the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed"). Thus, an applicant complies with the written-description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572.

6. For convenience, claims 9, 10, and 23, the only independent claims currently pending in the instant application, are reproduced below.

9. (currently amended) A method for inhibiting [[a]] an mRNA, comprising:

a) providing an ~~interfering hairpin~~ RNA ~~having~~ comprising the structure X_1-L-X_2, wherein X_1 and X_2 are nucleotide sequences having sufficient complementarity to one another to form a double-stranded stem hybrid and L is a flexible loop region comprising a non-nucleotide linker molecule of 10-24 atoms in length, wherein at least a portion of one of the nucleotide sequences located within the double-stranded stem is complementary to a sequence of ~~said~~ the target mRNA; and

b) contacting ~~shRNA~~ the RNA comprising the structure X_1-L-X_2 with a sample containing or suspected of containing the target mRNA under conditions that favor ~~intermolecular hybridization between~~ transfection of the ~~shRNA~~ RNA comprising the structure X_1-L-X_2 into a cell comprising the target mRNA ~~and the target mRNA~~ whereby presence of the ~~shRNA~~ RNA comprising the structure X_1-L-X_2 decreases expression of the target mRNA[[.]];

wherein X_1 and X_2 each independently comprise between about 19 to 27 nucleotides, and L comprises a polyether, a polyamine, a polyester, a polyphosphodiester, an alkylene, or a combination thereof.

10. (currently amended) A method for assaying whether a gene product is a suitable target for drug discovery comprising:

a) introducing an [[sh]]RNA which targets ~~the~~ an mRNA of ~~the~~ a gene for degradation into a cell or organism, wherein said [[sh]]RNA ~~having~~ comprises the structure X_1-L-X_2, wherein X_1 and X_2 are nucleotide sequences having sufficient complementarity to one another to form a double-stranded stem hybrid and L is a flexible loop region comprising a non-nucleotide linker molecule of 10-24 atoms in length, wherein at least a portion of one of the nucleotide sequences located within the double-stranded stem hybrid is complementary to a sequence of said ~~double-stranded RNA~~ mRNA, wherein X_1 and X_2 each independently comprise between about 19 to 27 nucleotides, and L comprises a polyether, a polyamine, a polyester, a polyphosphodiester, an alkylene, or a combination thereof;

b) maintaining the cell or organism of [[(]]a) under conditions in which degradation of the mRNA occurs, resulting in decreased expression of the gene; and

c) determining the effect of the decreased expression of the gene on the cell or organism, wherein if decreased expression has an effect, then the gene product is a target for drug discovery.

23. (New) A method for inhibiting a target mRNA, comprising:

a) providing an RNA comprising the structure X_1-L-X_2, wherein X_1 and X_2 are nucleotide sequences having sufficient complementarity to one another to form a double-stranded stem hybrid and L is a loop region comprising a non-nucleotide linker molecule, wherein at least a portion of one of the nucleotide sequences located within the double-stranded stem is complementary to a sequence of the target mRNA; and

b) contacting the RNA comprising the structure X_1-L-X_2 with a sample containing or suspected of containing the target mRNA under conditions that favor transfection of the RNA comprising the structure X_1-L-X_2 into a cell comprising the target mRNA whereby presence of the RNA comprising the structure X_1-L-X_2 decreases expression of the target mRNA;

wherein X_1 and X_2 each independently comprise between about 19 to 27 nucleotides; L comprises a polyether, a polyamine, a polyester, a polyphosphodiester, an alkylene, or a combination thereof; L is 10-24 atoms in length; the RNA comprising the structure X_1-L-X_2 comprises a left hairpin RNA; and the left hairpin RNA comprising the structure X_1-L-X_2 comprises an overhang of 1 to 5 nucleotides and at least one bulge.

7. Claims 9 and 11-23 are drawn to a method of inhibiting mRNA expression. For purposes of examination, said method has been interpreted as encompassing gene therapy in any life form and for any mRNA that is being translated. Claim 10, as evident above, is drawn to a method of assaying whether any gene product is a suitable target for drug discovery.

8. A review of the disclosure finds the following examples:

a. Example 1, "Hairpin Design," pages 11-14; and

b. Example 2, "Hairpin Design with different overhangs," pages 14-15."

9. None of the examples are drawn to the claimed methods. A review of the disclosure fails to find an adequate written description of how the two methods are to be practiced. With the claims encompassing performing the method *in* vivo, not just *in* vitro, the manner and means of

introducing RNA having the structure X_1-L-X_2 into any cell and have such transfection result in the desired end product is most difficult and unpredictable.

10. While applicant has amended the specification such that specific portions of cited documents are now identified, and amendment that raises the issue of new matter having been introduced in to the disclosure, *supra*, the disclosure still does not provide an adequate written description of how these methods are to be performed. It appears that applicant is attempting to satisfy the written description requirement of 35 USC 112, first paragraph, through obviousness. Obviousness, however, cannot be relied upon for satisfaction of the written description requirement. In support of this position, attention is directed to the decision in *University of California v. Eli Lilly and Co.* (Fed. Cir. 1997) 43 USPQ2d at 1405, citing *Lockwood v. American Airlines Inc.* (Fed. Cir. 1997) 41 USPQ2d at 1966:

> Recently, we held that a description which renders obvious a claimed invention is not sufficient to satisfy the written description requirement of that invention.

11. For the above reasons, and in the absence of convincing evidence to the contrary, claims 9-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Response to argument

12. At page 10 of the response received 27 September 2004, hereinafter the response, applicant's representative asserts that the Office has not stipulated how or why the recited structural limitations of the RNAs of the methods would depend on the identity of the target mRNA. Argument is also advanced at said page that "there is simply no need to list sequences

of target mRNAs in this application, nor is there a need to list sequences complementary to the target mRNAs, in order to satisfy the written description requirement."

13. The above argument ahs been fully considered and has not been found persuasive towards the withdrawal of the rejection. It is noted with particularity that the claims are not drawn to a generalized method of making mRNA that has the structure X_1-L-X_2 structure. Rather, the claims are drawn to a method of gene therapy as well as a method of identifying genes that would be suitable targets for drug discovery.

14. In both instances, the ability to selectively and effectively target the correct target gene is critical. The specification is essentially silent as to what these genes are and how one would be able to identify a suitable gene as compared to an unsuitable gene. Clearly, the structure of such a gene is of paramount importance, for at its heart, they are a series of nucleotides. The specification is silent as to how either method is to be practiced.

15. Argument is advanced at page 11 of the disclosure that "Applicant teaches in the specification as filed methods for using over 72 exemplary RNA molecules that permute recited structural limitations in the present claims using lamin A/C as a target mRNA."

16. The above argument has been fully considered and has not been found persuasive. A review of the papers filed fails to locate any sequence listing, be it paper of computer readable. Further, the specification provides but two examples, and neither is directed to the use of any such sequences. It is noted that page 16 of the specification provides a brief synopsis of an assay, relevant portions of which are reproduced below.

The silencing of the lamin A/C gene by RNA interference with the shRNAs or control duplexes were examined. The results are shown in Figures 6 and 7. In Figure 6 the results are plotted by grouping hairpins of the same core length, and Figure 7 shows the same results but grouped according to the type of overhang. The percent inhibition in Figures 6 and 7 is

The aspect of teaching that some aspect was "examined" does not provide an adequate written description of just how the assay is to be performed for any and all life forms, including humans, when as noted at page 16, lines 12-13, toxicity to cells was observed.

17. For the above reasons, and in the absence of convincing evidence to the contrary, claims 9-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Claims 9-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

> To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, *e.g.*, *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re*

> *Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

18. The specification teaches that the claimed method is to employ short interfering hairpin RNA in a variety of methods, including the treatment of any "plant, animal or human suspected of having or being prone to a disease or condition associated with expression of a target gene" (page 4 second paragraph, of the specification). Said methods of inhibiting mRNA (claims 9 and 11-23) have also been interpreted as fairly encompassing the "knocking down (partially or completely) a targeted gene, for example for generating models of disease states, to examine the function of a gene, to assess whether an agent acts on a gene, to validate targets for drug discovery, etc." (Specification at page 10, fist paragraph).

19. A review of the disclosure fails to find where any one, much less all of the intended utilities have been fully enabled by the specification, regardless of whether they are to be gene therapy, or the identification of a gene as a suitable target for drug development.

20. The specification fails to set forth the requisite starting materials and reaction conditions that would permit one of skill in the art at the time the invention was made to reproducibly manufacture any and all useful interfering hairpin RNA molecules. While the specification makes reference to various documents, and the specification has been amended so to recite relevant portions of some of these documents (supra), the disclosure, even when amended, still

does not provide the requisite starting materials and reaction conditions. As noted above, the method of claims 9 and 11-23 fairly encompass gene therapy in any individual, including a human. The specification is silent as to what drugs (mRNA sequences) are to be sued, and how these sequences are to be introduced, into any subject, much less be caused to selectively diminish mRNA transcription without resulting in toxicity to the cell/individual (specification at page 16). The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

> " '[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').
>
> *****
>
> "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (starting, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.
> "It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. <u>However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art.</u> It is the

> specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research. (Emphasis added)

21. With no specific starting material or reaction conditions provided, the skilled artisan would have to resort to trial and error experimentation with little if any reasonable expectation of success. Such level of effort required to the exerted by the skilled artisan is undue. Therefore, and in the absence of convincing evidence to the contrary, claims 9-23 are rejected under 35 USC 112, first paragraph, as failing to comply with the enablement requirement.

Response to argument

22. Agreement is reached with applicant's representative in that one need not teach that which is well known. In the present case, there is no convincing evidence to record that established just what the level of skill is in the art. Attention is directed to MPEP 2145.

> Attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See MPEP § 2129 and § 2144.03 for a discussion of admissions as prior art.
> The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness."). See MPEP § 716.01(c) for examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration.

23. It is noted that applicant's representative has referred to paragraph by number (response at page 13), however, it is not readily apparent just which paragraphs said representative is referring to as the specification originally filed lacked such identifiers, but does contain both page and line numbers.

24. At page 13, bridging to page 14 of the disclosure argument is advanced that the level of skill in the art was such that one could make mRNA with hairpin structures with non-nucleotide linkers, and s such, the claimed method are enabled by the disclosure.

25. The above argument has been fully considered and ahs not been found persuasive for the claimed invention is not a method of making mRNA with a hairpin structure and comprising a non-nucleotide linker, but rather, being able take the correct such mRNA complex and use it in an admittedly novel and non-obvious manner to effect gene therapy in any and all manner of organisms, a well as inhibit mRNA translation for any gene(s) in an *in vitro* environment. Additionally, the method of claim 10 requires one to be able to identify genes that are suitable targets for drug development. A review of the disclosure and applicant's representative's arguments fail to address how one would be able to identify such candidate genes, nor how to identify and use the appropriate inhibiting mRNA.

26. Therefore, and in the absence of convincing evidence to the contrary, claims 9-23 are rejected under 35 USC 112, first paragraph, as failing to comply with the enablement requirement.

Conclusion

27. Rejections and/or objections that appeared in the prior Office action and not repeated hereinabove have been withdrawn.

28. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

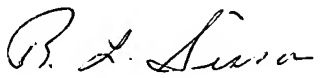
29. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571) 272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

31. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (571) 272-0745. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

32. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS
24 January 2005